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L1 983 VEGF-D

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L2 13 L1 AND BRAIN TUMOR

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PROCESSING COMPLETED FOR L2
L3 5 DUP REMOVE L2 (8 DUPLICATES REMOVED)

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L3 ANSWER 1 OF 5 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 1
2005:428915 The Genuine Article (R) Number: 917EQ. Fos-related antigen 1 modulates malignant features of glioma cells. Debinski W (Reprint); Gibo D M. Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Med Ctr Blvd, Winston Salem, NC 27157 USA (Reprint); Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest Univ, Sch Med, Dept Radiat Oncol, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest Univ, Sch Med, Dept Canc Biol, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA. debinski@wfubine.edu. MOLECULAR CANCER RESEARCH (APR 2005) Vol. 3, No. 4, pp. 237-249. ISSN: 1541-7786. Publisher: AMER ASSOC CANCER RESEARCH, 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Malignant gliomas, and high-grade gliomas (HGG) in particular, are non metastasizing but locally infiltrating, hypervascularized **brain tumors** of poor prognosis. We found previously that a c-fos-inducible vascular endothelial growth factor D is ubiquitously up-regulated in HGG grade IV, glioblastoma multiforme, and that glioblastoma multiforme overexpress Fos-related antigen 1 (Fra-1) rather than the c-Fos. We have thus become interested in the role Fra-1 may play in malignant glioma progression/maintenance, because Fra-1 has the capacity to modulate transcription of a variety of target genes. In this work, we have analyzed the biological effects of ectopic Fra-1 expression or Fra-1 knockdown in malignant glioma cells. Ectopic Fra-1 induced prominent phenotypic changes in all three malignant glioma cell lines examined: H4, U-87 MG, and A-172 MG. These changes were reflected in cells becoming more elongated with larger number of cellular processes. Furthermore, Fra-1 transgene caused H4 cells, which do not form tumor xenografts, to regain tumorigenic capacity. The genotype of these cells changed too, because 50 of 1,056 genes examined became either up- or down-regulated. Conversely, Fra-1 knockdown altered prominently the morphology, anchorage-independent growth, tumorigenic potential, and Fra-1 effector expression, such as vascular endothelial growth factor D, in HGG cells. For example, cells transfected with antisense fra-1 showed shorter cellular processes than the control cells that did not grow in agar, and their tumorigenic potential was significantly diminished. Thus, Fra-1 may likely play an important role in the maintenance/progression of malignant gliomas and potentially represents a new target for therapeutic interventions.

L3 ANSWER 2 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2005:124071 Document No.: PREV200500122163. 1st European Conference on Tumor

Angiogenesis and Antiangiogenic Therapy, Munich, Germany, October 1-3, 2004. Anonymous. Angiogenesis, (2004) Vol. 7, No. Suppl. 1, pp. 1-53. print.
Meeting Info.: 1st European Conference on Tumor Angiogenesis and Antiangiogenic Therapy. Munich, Germany. October 01-03, 2004.
ISSN: 0969-6970 (ISSN print). Language: English.

AB This meeting on angiogenesis consists of 2 keynote lectures, 26 oral presentations and 64 meeting posters written in English. Different cancer types, together with their pathology, drug therapy, radiotherapy, prevention and control and gene therapy are discussed. Other topics include tumor metastasis, embryonic lymphangiogenesis, growth factor regulation and microvessel density. Tumor phenotype, drug development and antiangiogenic effect are also discussed.

L3 ANSWER 3 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2003:492648 Document No.: PREV200300487100. Epigenetics in high-grade astrocytomas: Opportunities for prevention and detection of **brain tumors**. Debinski, Waldemar [Reprint Author]; Gibo, Denise; Mintz, Akiva. Section of Neurosurgery, Department of Surgery, College of Medicine, Pennsylvania State University, 500 University Drive, H110, Hershey, PA, 17033-0850, USA. wdebinski@psu.edu. Verma, Mukesh [Editor, Reprint Author]; Dunn, Barbara K. [Editor, Reprint Author]; Umar, Asad [Editor, Reprint Author]. (2003) pp. 232-242. Epigenetics in cancer prevention: Early detection and risk assessment. print. Publisher: New York Academy of Sciences, 2 East 63rd Street, New York, NY, 10021, USA. Series: Annals of the New York Academy of Sciences.
Meeting Info.: Workshop on Epigenetics in Cancer Prevention: Early Detection and Risk Assessment. Bethesda, MD, USA. December 03-04, 2001. National Institutes of Health (NIH).
ISSN: 0077-8923 (ISSN print). ISBN: 1-57331-430-7 (cloth). Language: English.

L3 ANSWER 4 OF 5 MEDLINE on STN DUPLICATE 2
2003204925. PubMed ID: 12724228. Epigenetics in high-grade astrocytomas: opportunities for prevention and detection of **brain tumors**. Debinski Waldemar; Gibo Denise; Mintz Akiva. (Department of Neurosurgery, Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033-0850, USA.. wdebinski@psu.edu) . Annals of the New York Academy of Sciences, (2003 Mar) 983 232-42. Ref: 60. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB Human high-grade astrocytomas (HGA) are the most prevalent incurable **brain tumors**. We found that the vast majority of HGA patients overexpress a restricted receptor for an immune regulatory cytokine, interleukin 13 (IL-13). Interestingly, the HGA-associated restricted receptor protein IL-13Ralpha2 is expressed in the testes, and its gene is localized to chromosome X. These mirror the expression pattern and genomic localization of cancer/testes tumor antigens (CTA). Hypothetical considerations and now experimental evidence are beginning to point towards epigenetics, and DNA methylation alterations in particular, as being responsible for the appearance in cancer of CTA, including IL-13Ralpha2. In line with our interest in the X chromosome and oncogenesis, we have identified a new ubiquitous angiogenic factor in HGA, a vascular endothelial growth factor-D (**VEGF-D**). We have also demonstrated that the activating protein-1 (AP-1) family of transcription factors play a potentially critical role in the progression of gliomas by eliciting uncontrolled upregulation of **VEGF-D** and other compounds essential for cancer cell proliferation, tumorigenesis, and infiltration. The possibility exists that an unopposed constitutive increase in AP-1 activity in HGA is related to epigenetic silencing of the inhibitors of AP-1 activity. These phenomena offer potential targets for exploitation in either prevention or early detection of **brain tumors**. For example, anticancer vaccines against shared CTA could help in prevention of HGA development. Furthermore, drugs with anti-AP-1 activity could be effective in

preventing formation/progression of HGA, or progression from less malignant lower grade gliomas to HGA. Also, circulating antibodies against CTA and factors that are AP-1 regulated may provide a useful tool in early detection of **brain tumors** or for monitoring their progression following initial treatment.

L3 ANSWER 5 OF 5 MEDLINE on STN DUPLICATE 3
2002052394. PubMed ID: 11778649. **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. Debinski W; Slagle-Webb B; Achen M G; Stacker S A; Tulchinsky E; Gillespie G Y; Gibo D M. (Division of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psu.edu) . Molecular medicine (Cambridge, Mass.), (2001 Sep) 7 (9) 598-608. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.

AB BACKGROUND: Glioblastoma multiforme (GBM) is a hypervascularized and locally infiltrating **brain tumor** of astroglial origin with a very poor prognosis. An X-linked c-fos oncogene-inducible mitogenic, morphogenic, and angiogenic factor, endothelial growth factor-D (**VEGF-D**), is the newest mammalian member of VEGF family. We analyzed **VEGF-D** in GBM because of its high angiogenic potential and its linkage to the X chromosome. MATERIALS AND METHODS: Nonmalignant brain and GBM tissue sections as well as GBM cell lines were analyzed by immunofluorescence for the expression of **VEGF-D**, factor VIII (endothelial cell marker), glial-fibrillary acidic protein (GFAP) (astrocytic cell lineage cytoplasmic marker), and several Fos family transcription factors, including c-Fos and Fra-1. The proteins were also detected by Western blots. The differences between genotypes of normal brain and GBM cells were examined by cDNA microarrays. RESULTS AND CONCLUSIONS: GBM expressed ubiquitously **VEGF-D**, which colocalized with GFAP. Contrary to our expectations, low levels of c-Fos were detected in GBM cells. However, we identified another Fos family member, Fra-1, together with its transcriptional activation partner, c-Jun, as being stably up-regulated in GBM cells. Furthermore, we demonstrated that a fra-1 transgene induced **VEGF-D** expression in cultured cells and GBM cell stimulation evoked a sustained increase in both Fra-1 and **VEGF-D** levels. This study reveals that an up-regulation of AP-1 factors may be a hallmark of GBM. Because **VEGF-D** activates VEGF receptor 2 and 3, receptors important for tumor angiogenesis, it may represent an X-linked/AP-1-regulated onco-angiogen in human GBM. The **VEGF-D** system and AP-1 activity appear to be very attractive targets for new molecular diagnostics and rational molecular anti-cancer therapies.

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L5          970 L4 AND VEGF

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L6           16 L5 AND VEGF-D

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L7             9 DUP REMOVE L6 (7 DUPLICATES REMOVED)

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L7 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
2005:540647 Document No. 143:90991 Single-domain protein inhibitors of type 2 vascular endothelial growth factor receptors for treatment of hyperproliferative disorders. Chen, Yan; Getmanova, Elena; Wright, Martin

C.; Harris, Al; Lim, Ai Ching; Gokemeijer, Jochim (Compound Therapeutics, Inc., USA). PCT Int. Appl. WO 2005056764 A2 20050623, 136 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US40885 20041206. PRIORITY: US 2003-2003/PV527886 20031205.

AB The present disclosure relates to novel vascular endothelial growth factor receptor (VEGFR)-binding polypeptides and methods for using these polypeptides to inhibit biol. signaling mediated by vascular endothelial growth factors (**VEGFs**). These VEGFR-inhibiting polypeptides may be used to inhibit hyperproliferative disorders, e.g., autoimmune disorders, inflammatory disorders, retinopathy, and cancers. Thus, sequence variants of human fibronectin III domain 3 were prepared Some of the variants inhibited **VEGF** binding to VEGFR2 with picomolar KD. Such proteins also inhibited VEGFR2 signaling in mammalian cells and inhibited growth of melanoma and **glioblastoma** cells in vivo. PEGylation of these proteins improved their pharmacokinetics.

L7 ANSWER 2 OF 9 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 1

2005:428915 The Genuine Article (R) Number: 917EQ. Fos-related antigen 1 modulates malignant features of glioma cells. Debinski W (Reprint); Gibo D M. Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Med Ctr Blvd, Winston Salem, NC 27157 USA (Reprint); Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest Univ, Sch Med, Dept Radiat Oncol, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest Univ, Sch Med, Dept Canc Biol, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA. debinski@wfubine.edu. MOLECULAR CANCER RESEARCH (APR 2005) Vol. 3, No. 4, pp. 237-249. ISSN: 1541-7786. Publisher: AMER ASSOC CANCER RESEARCH, 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Malignant gliomas, and high-grade gliomas (HGG) in particular, are non metastasizing but locally infiltrating, hypervascularized brain tumors of poor prognosis. We found previously that a c-fos-inducible vascular endothelial growth factor D is ubiquitously up-regulated in HGG grade IV, **glioblastoma** multiforme, and that **glioblastoma** multiforme overexpress Fos-related antigen 1 (Fra-1) rather than the c-Fos. We have thus become interested in the role Fra-1 may play in malignant glioma progression/maintenance, because Fra-1 has the capacity to modulate transcription of a variety of target genes. In this work, we have analyzed the biological effects of ectopic Fra-1 expression or Fra-1 knockdown in malignant glioma cells. Ectopic Fra-1 induced prominent phenotypic changes in all three malignant glioma cell lines examined: H4, U-87 MG, and A-172 MG. These changes were reflected in cells becoming more elongated with larger number of cellular processes. Furthermore, Fra-1 transgene caused H4 cells, which do not form tumor xenografts, to regain tumorigenic capacity. The genotype of these cells changed too, because 50 of 1,056 genes examined became either up- or down-regulated. Conversely, Fra-1 knockdown altered prominently the morphology, anchorage-independent growth, tumorigenic potential, and Fra-1 effector expression, such as vascular endothelial growth factor D, in HGG cells. For example, cells transfected with antisense fra-1 showed shorter cellular processes than the control cells that did not grow in agar, and their tumorigenic potential was significantly diminished. Thus, Fra-1 may likely play an important role in the maintenance/progression of malignant gliomas and potentially represents a new target for therapeutic interventions.

L7 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN

2002:793426 Document No. 137:310925 Preparation of 3-(azahetero)aryl-1H-pyrazolo[3,4-d]pyrimidin-3-amines as protein kinase inhibitors with antiangiogenic properties. Hirst, Gavin C.; Rafferty, Paul; Ritter, Kurt; Calderwood, David; Wishart, Neil; Arnold, Lee D.; Friedman, Michael M. (Abbott G.m.b.H. & Co. K.-G., Germany). PCT Int. Appl. WO 2002080926 A1 20021017, 867 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US9104 20020322. PRIORITY: US 2001-2001/815310 20010322.

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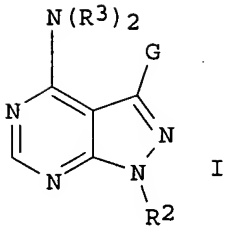

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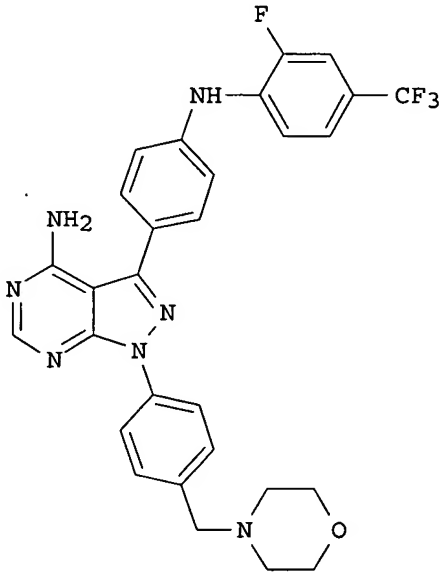

II

AB Title compds. I [wherein G = (un)substituted 5-6 membered (azahetero)aryl; R2 = H or (un)substituted trityl, cycloalkenyl, azaheteroaryl, or C6H4-4-CH2E; E = (un)substituted alkyl-OR, alkyl-CO2R, alkylheteroaryl, alkylheterocycloalkyl, or alkyl-NR2; R = independently H or (un)substituted (cyclo)alkyl, or aryl(alkyl); R3 = independently H, OH, or (un)substituted alkyl, alkyl-CO, (hetero)aryl-CO, or alkoxy; or racemic diastereomeric mixts., optical isomers, pharmaceutically acceptable salts, prodrugs, and/or biol. active metabolites thereof] were prepared For example, 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine was coupled with 4-fluorobenzaldehyde in the presence of NaH in DMF to give 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzaldehyde. Treatment of the 3-iodopyrazolopyrimidine with N-[2-methoxy-4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-(trifluoromethyl)benzamide, Pd(PPh3)4, and Na2CO3 in H2O afforded the N-[4-(pyrazolopyrimidin-3-yl)phenyl]benzamide. Addition of morpholine to the benzaldehyde in the presence of Na(AcO)3BH in dichloroethane produced II. All exemplified compds. significantly inhibited either FGFR, PDGFR, KDR, Tie-2, Lck, Fyn, Blk, Lyn, or Src at concentration of ≤ 50 μM. Certain compds. of the invention also significantly inhibited cdc2 or cellular

VEGF-induced KDR tyrosine kinase phosphorylation at concns. of ≤ 50 μM. Thus, I are useful for the treatment of a wide variety of disease states ameliorated by the inhibition of protein tyrosine kinase activity essential for angiogenic processes (no data).

L7 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN

2002:754390 Document No. 137:263056 Preparation of 3-(azahetero)aryl-1H-pyrazolo[3,4-d]pyrimidin-3-amines as protein kinase inhibitors with antiangiogenic properties. Hirst, Gavin C.; Rafferty, Paul; Ritter, Kurt; Calderwood, David; Wishart, Neil; Arnold, Lee D.; Friedman, Michael M. (Abbott GmbH & Co. KG, Germany). PCT Int. Appl. WO 2002076986 A1 20021003, 440 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US8996 20020322. PRIORITY: US 2001-2001/PV278047 20010322.

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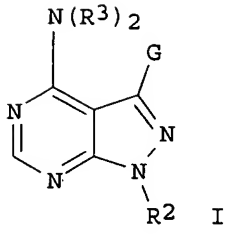

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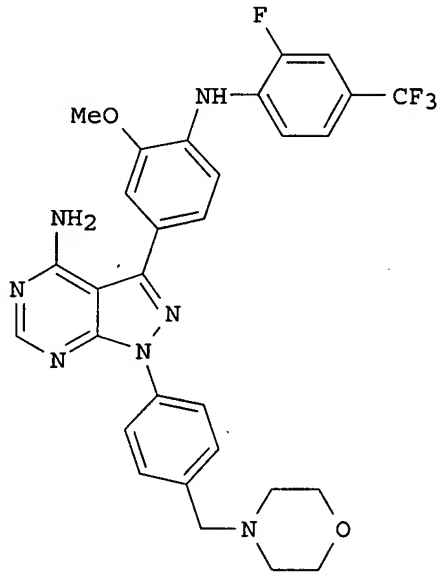

II

AB Title compds. I [wherein G = (un)substituted 5-6 membered (azahetero)aryl; R2 = H or (un)substituted trityl, cycloalkenyl, azaheteroaryl, or C6H4-4-CH2E; E = (un)substituted alkyl-OR, alkyl-CO2R, alkylheteroaryl, alkylheterocycloalkyl, or alkyl-NR2; R = independently H or (un)substituted (cyclo)alkyl, or aryl(alkyl); R3 = independently H, OH, or (un)substituted alkyl, alkyl-CO, (hetero)aryl-CO, or alkoxy; or racemic diastereomeric mixts., optical isomers, pharmaceutically acceptable salts, prodrugs, and/or biol. active metabolites thereof] were prepared For example, 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine was coupled with 4-fluorobenzaldehyde in the presence of NaH in DMF to give 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzaldehyde. Treatment of the 3-iodopyrazolopyrimidine with N-[2-methoxy-4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-(trifluoromethyl)benzamide, Pd(PPh3)4, and Na2CO3 in H2O afforded the N-[4-(pyrazolopyrimidin-3-yl)phenyl]benzamide. Addition of morpholine to the

benzaldehyde in the presence of Na(AcO)3BH in dichloroethane produced II. All exemplified compds. significantly inhibited either FGFR, PDGFR, KDR, Tie-2, Lck, Fyn, Blk, Lyn, or Src at concentration of ≤ 50 μM. Certain compds. of the invention also significantly inhibited cdc2 or cellular **VEGF**-induced KDR tyrosine kinase phosphorylation at concns. of ≤ 50 μM. Thus, I are useful for the treatment of a wide variety of disease states ameliorated by the inhibition of protein tyrosine kinase activity essential for angiogenic processes (no data).

L7 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN

2002:637486 Document No. 137:164115 **VEGF-D** expression in brain cancer in relation to diagnosis and treatment. Debinski, Waldemar; Gibo, Denise M. (The Penn State Research Foundation, USA). PCT Int. Appl. WO 2002064097 A2 20020822, 43 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US5044 20020212. PRIORITY: US 2001-PV268089 20010212.

AB **VEGF-D** serves as a target for diagnosing and treating **glioblastoma** multiforme and related brain cancers. Cancer in a brain tissue sample is detected by analyzing expression of **VEGF-D** in the sample. Brain cancer is treated by modulating **VEGF-D** gene expression in cells of the cancer, and by inhibiting angiogenesis associated with the cancer by interfering with **VEGF-D** binding to a **VEGF-D** receptor.

L7 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN

2002:814851 Document No. 137:310930 Preparation of 3-(azahetero)aryl-1H-pyrazolo[3,4-d]pyrimidin-3-amines as protein kinase inhibitors with antiangiogenic properties. Hirst, Gavin C.; Rafferty, Paul; Ritter, Kurt; Calderwood, David; Wishart, Neil; Arnold, Lee D.; Friedman, Michael M. (Abbott Laboratories, USA). U.S. Pat. Appl. Publ. US 2002156081 A1 20021024, 426 pp., Cont.-in-part of U.S. Ser. No. 663,780. (English). CODEN: USXXCO. APPLICATION: US 2001-815310 20010322. PRIORITY: US 1999-PV154620 19990917; US 2000-2000/663780 20000915.

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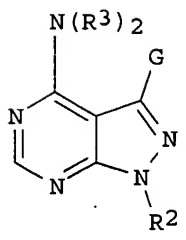

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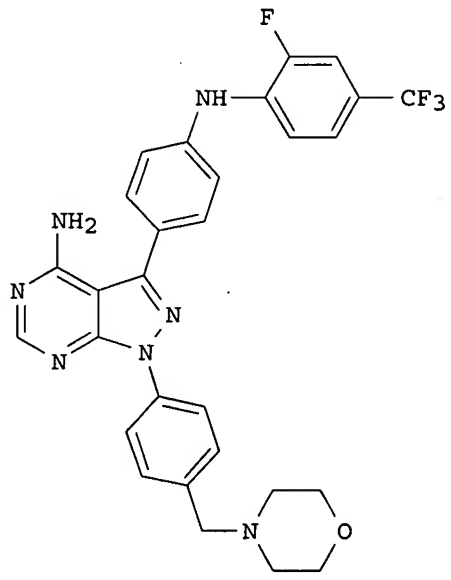

II

AB Title compds. I [wherein G = (un)substituted 5-6 membered (azahetero)aryl; R2 = H or (un)substituted trityl, cycloalkenyl, azaheteroaryl, or C6H4-4-CH2E; E = (un)substituted alkyl-OR, alkyl-CO2R, alkylheteroaryl, alkylheterocycloalkyl, or alkyl-NR2; R = independently H or (un)substituted (cyclo)alkyl, or aryl(alkyl); R3 = independently H, OH, or (un)substituted alkyl, alkyl-CO, (hetero)aryl-CO, or alkoxy; or racemic diastereomeric mixts., optical isomers, pharmaceutically acceptable salts, prodrugs, and/or biol. active metabolites thereof] were prepared For example, 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine was coupled with 4-fluorobenzaldehyde in the presence of NaH in DMF to give 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzaldehyde. Treatment of the 3-iodopyrazolopyrimidine with N-[2-methoxy-4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-(trifluoromethyl)benzamide, Pd(PPh3)4, and Na2CO3 in H2O afforded the N-[4-(pyrazolopyrimidin-3-yl)phenyl]benzamide. Addition of morpholine to the benzaldehyde in the presence of Na(AcO)3BH in dichloroethane produced II. All exemplified compds. significantly inhibited either FGFR, PDGFR, KDR, Tie-2, Lck, Fyn, Blk, Lyn, or Src at concentration of ≤ 50 μM. Certain compds. of the invention also significantly inhibited cdc2 or cellular **VEGF**-induced KDR tyrosine kinase phosphorylation at concns. of ≤ 50 μM. Thus, I are useful for the treatment of a wide variety of disease states ameliorated by the inhibition of protein tyrosine kinase activity essential for angiogenic processes (no data).

L7 ANSWER 7 OF 9 MEDLINE on STN DUPLICATE 2

2003109214. PubMed ID: 12622137. Histone deacetylase inhibitors such as sodium butyrate and trichostatin A inhibit vascular endothelial growth factor (**VEGF**) secretion from human **glioblastoma** cells.
Sawa Hiroki; Murakami Hiromi; Ohshima Yuko; Murakami Masahiro; Yamazaki Ichiro; Tamura Yasuo; Mima Tatsuo; Satone Akira; Ide Wataru; Hashimoto Ikuo; Kamada Hajime. (Oncology Research Center, Hokuto Hospital, Kisen 7-5, Inada-cho, Obihiro, Hokkaido 080-0833, Japan.. sawa@hokuto7.or.jp) .
Brain tumor pathology, (2002) 19 (2) 77-81. Journal code: 9716507. ISSN: 1433-7398. Pub. country: Japan. Language: English.

AB We investigated the effects of histone deacetylase (HDAC) inhibitors such as sodium butyrate (SB) and trichostatin A (TSA) on the expression of vascular endothelial growth factor (**VEGF**) by human **glioblastoma** T98G, U251MG, and U87MG cells. The **glioblastoma** cells secreted three **VEGF** isoforms, **VEGF** (189), (165), and (121), although the expression levels of **VEGF** differed between the cell types. Treatment with either 5mM SB or 100 ng/ml TSA reduced **VEGF** secretion in conditioned media and reduced **VEGF** mRNA expression. We also studied the expression of **VEGF**-B, -C, and -D mRNA in human **glioblastoma** cells and their modulation by HDAC inhibitors. The PCR products of **VEGF**-B (357bp), **VEGF**-C (501bp), and **VEGF-D** (484bp) were amplified in all **glioblastoma** cells examined. Treatment with SB reduced the expression of **VEGF-D** mRNA in U251MG cells and the expression of **VEGF**-B mRNA in U87MG cells. TSA treatment reduced the expression of **VEGF-D** in U251MG cells. These results suggest that HDAC inhibitors reduce **VEGF** secretion and modulate the expression of the other **VEGF** family members, and therefore may inhibit angiogenesis in **glioblastoma** tissues.

L7 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN

2003:439275 Document No. 139:83053 **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human **glioblastoma** multiforme. [Erratum to document cited in CA136:322910]. Debinski, Waldemar; Slagle-Webb, Becky; Achen, Marc G.; Stacker, Steven A.; Tulchinsky, Eugene; Gillespie, G. Yancey; Gibo, Denise M. (Division of Neurosurgery/H110, Pennsylvania State University College of Medicine, Hershey, PA, 17033-0850, USA). Molecular Medicine (Baltimore, MD, United States), 7(12), 861 (English) 2001. CODEN: MOMEF3.

ISSN: 1076-1551. Publisher: Johns Hopkins University Press.
AB On the cover, "mutliforme" should be "multiforme".

L7 ANSWER 9 OF 9 MEDLINE on STN DUPLICATE 3
2002052394. PubMed ID: 11778649. **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human **glioblastoma** multiforme. Debinski W; Slagle-Webb B; Achen M G; Stacker S A; Tulchinsky E; Gillespie G Y; Gibo D M. (Division of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psu.edu) . Molecular medicine (Cambridge, Mass.), (2001 Sep) 7 (9) 598-608. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.
AB BACKGROUND: **Glioblastoma** multiforme (GBM) is a hypervascularized and locally infiltrating brain tumor of astroglial origin with a very poor prognosis. An X-linked c-fos oncogene-inducible mitogenic, morphogenic, and angiogenic factor, endothelial growth factor-D (**VEGF-D**), is the newest mammalian member of **VEGF** family. We analyzed **VEGF-D** in GBM because of its high angiogenic potential and its linkage to the X chromosome. MATERIALS AND METHODS: Nonmalignant brain and GBM tissue sections as well as GBM cell lines were analyzed by immunofluorescence for the expression of **VEGF-D**, factor VIII (endothelial cell marker), glial-fibrillary acidic protein (GFAP) (astrocytic cell lineage cytoplasmic marker), and several Fos family transcription factors, including c-Fos and Fra-1. The proteins were also detected by Western blots. The differences between genotypes of normal brain and GBM cells were examined by cDNA microarrays. RESULTS AND CONCLUSIONS: GBM expressed ubiquitously **VEGF-D**, which colocalized with GFAP. Contrary to our expectations, low levels of c-Fos were detected in GBM cells. However, we identified another Fos family member, Fra-1, together with its transcriptional activation partner, c-Jun, as being stably up-regulated in GBM cells. Furthermore, we demonstrated that a fra-1 transgene induced **VEGF-D** expression in cultured cells and GBM cell stimulation evoked a sustained increase in both Fra-1 and **VEGF-D** levels. This study reveals that an up-regulation of AP-1 factors may be a hallmark of GBM. Because **VEGF-D** activates **VEGF** receptor 2 and 3, receptors important for tumor angiogenesis, it may represent an X-linked/AP-1-regulated onco-angiogen in human GBM. The **VEGF-D** system and AP-1 activity appear to be very attractive targets for new molecular diagnostics and rational molecular anti-cancer therapies.

=> s (debinski w?/au)
L8 517 (DEBINSKI W?/AU)

=> s l8 and brain cancer
L9 15 L8 AND BRAIN CANCER

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L10 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
2002:637486 Document No. 137:164115 VEGF-D expression in **brain cancer** in relation to diagnosis and treatment. **Debinski, Waldemar**; Gibo, Denise M. (The Penn State Research Foundation, USA). PCT Int. Appl. WO 2002064097 A2 20020822, 43 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF,

BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US5044 20020212. PRIORITY: US 2001-PV268089 20010212.

AB VEGF-D serves as a target for diagnosing and treating glioblastoma multiforme and related **brain cancers.** Cancer in a brain tissue sample is detected by analyzing expression of VEGF-D in the sample. **Brain cancer** is treated by modulating VEGF-D gene expression in cells of the cancer, and by inhibiting angiogenesis associated with the cancer by interfering with VEGF-D binding to a VEGF-D receptor.

L10 ANSWER 2 OF 4 MEDLINE on STN DUPLICATE 1

1998250014. PubMed ID: 9590132. Novel way to increase targeting specificity to a human glioblastoma-associated receptor for interleukin 13. **Debinski W**; Gibo D M; Puri R K. (Section of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@PSGHS.EDU) . International journal of cancer. Journal international du cancer, (1998 May 18) 76 (4) 547-51. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB Human **brain cancers** (gliomas) overexpress large numbers of a receptor for interleukin 13 (IL13), making this receptor an attractive target for anti-glioma therapies. We have recently proposed that the glioma-associated IL13 receptor is different from the one expressed on some hemopoietic and somatic cells. In an attempt to identify an even more glioma-specific target, we have used an antagonist of a related cytokine, IL4, which neutralizes the physiological effects of both IL13 and IL4 on normal cells. Here we demonstrate that the IL4 antagonist also counteracts the action of cytotoxins targeted to the IL13 receptor on normal human cells. Importantly, the IL4 antagonist does not inhibit IL13-based cytotoxins on glioma cells at all. Thus, the IL13 receptor on glioma cells can be categorized as tumor-specific in the presence of an IL4 antagonist. We conclude that IL13 receptor-directed cytotoxins can be delivered to glioma cells without being cytotoxic to normal cells.

L10 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 2

1998254729. PubMed ID: 9592393. Novel anti-brain tumor cytotoxins specific for cancer cells. **Debinski W**; Gibo D M; Obiri N I; Kealiher A; Puri R K. (Department of Surgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psghs.edu) . Nature biotechnology, (1998 May) 16 (5) 449-53. Journal code: 9604648. ISSN: 1087-0156. Pub. country: United States. Language: English.

AB The vast majority of **brain cancers** (gliomas) express a receptor (R) for interleukin 13 (IL13). In order to achieve specific targeting of the IL13R in gliomas, we have mutagenized human (h) IL13. The mutation was made to alter IL13 interaction with the shared functional IL13/4 normal tissue receptor, but not with the glioma-associated receptor. We have thus produced hIL13.E13K (glutamic acid at position 13 changed to lysine) and fused it to derivatives of Pseudomonas exotoxin A. The hIL13.E13K-based cytotoxins are less active on normal cells and thus less toxic, and are better antitumor agents compared with the cytotoxins containing nonmutagenized hIL13.

L10 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 3

1999034937. PubMed ID: 9815919. Human glioma cells overexpress receptors for interleukin 13 and are extremely sensitive to a novel chimeric protein composed of interleukin 13 and pseudomonas exotoxin. **Debinski W**; Obiri N I; Powers S K; Pastan I; Puri R K. (The Milton S. Hershey Medical Center, The Pennsylvania State University College of Medicine, Department of Surgery, Division of Neurosurgery, Hershey, Pennsylvania 17033, USA.. debinski@debin.nsr.hmc.psu.edu) . Clinical cancer research : an official journal of the American Association for Cancer Research, (1995 Nov) 1 (11) 1253-8. Journal code: 9502500. ISSN: 1078-0432. Pub. country: United States. Language: English.

AB Recently, we have demonstrated that a spectrum of human adenocarcinoma cell lines express binding sites for interleukin 13 (IL-13). These cells are killed by a chimeric protein composed of human (h) IL-13 and a derivative of Pseudomonas exotoxin, PE38QQR (Debinski et al., J. Biol. Chemical, 270: 16775-16780, 1995). The cell killing was hIL-13- and hIL-4-specific, indicating that a common binding site for the two cytokines is present in several solid tumor cell lines. Herein, we report that an array of established glioma cell lines is killed by very low concentrations of hIL-13-PE38QQR, often reaching <1 ng/ml (<20 pM). Glioma cells express up to 30,000 molecules of IL-13 receptor/cell which has intermediate affinity toward hIL-13. hIL-13-PE38QQR is more active (up to 3 logs difference in cytotoxic activities) than are the corresponding chimeric toxins containing hIL-4 or hIL-6. The cytotoxic action of hIL-13-PE38QQR is blocked by an excess of hIL-13 on all cell lines studied, and it is not neutralized by hIL-4 on some of these cells. Our results show that human **brain cancers** richly express receptors for IL-13. Furthermore, the interaction detected previously between receptors for IL-13 and IL-4 on solid tumors cell lines is of a qualitatively different character in U-251 MG and U-373 MG glioma cells. The receptor for IL-13 may represent a new marker of **brain cancers** and an attractive target for anticancer therapies.

=> s l8 and VEGF-D
L11 14 L8 AND VEGF-D

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PROCESSING COMPLETED FOR L11
L12 6 DUP REMOVE L11 (8 DUPLICATES REMOVED)

=> d l12 1-6 cbib abs

L12 ANSWER 1 OF 6 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 1
2005:428915 The Genuine Article (R) Number: 917EQ. Fos-related antigen 1 modulates malignant features of glioma cells. **Debinski W (Reprint)**; Gibo D M. Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Med Ctr Blvd, Winston Salem, NC 27157 USA (Reprint); Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest Univ, Sch Med, Dept Radiat Oncol, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest Univ, Sch Med, Dept Canc Biol, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA. debinski@wfubine.edu. MOLECULAR CANCER RESEARCH (APR 2005) Vol. 3, No. 4, pp. 237-249. ISSN: 1541-7786. Publisher: AMER ASSOC CANCER RESEARCH, 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Malignant gliomas, and high-grade gliomas (HGG) in particular, are non metastasizing but locally infiltrating, hypervascularized brain tumors of poor prognosis. We found previously that a c-fos-inducible vascular endothelial growth factor D is ubiquitously up-regulated in HGG grade IV, glioblastoma multiforme, and that glioblastoma multiforme overexpress Fos-related antigen 1 (Fra-1) rather than the c-Fos. We have thus become interested in the role Fra-1 may play in malignant glioma progression/maintenance, because Fra-1 has the capacity to modulate transcription of a variety of target genes. In this work, we have analyzed the biological effects of ectopic Fra-1 expression or Fra-1 knockdown in malignant glioma cells. Ectopic Fra-1 induced prominent phenotypic changes in all three malignant glioma cell lines examined: H4, U-87 MG, and A-172 MG. These changes were reflected in cells becoming more elongated with larger number of cellular processes. Furthermore, Fra-1 transgene caused H4 cells, which do not form tumor xenografts, to regain tumorigenic capacity. The genotype of these cells changed too, because 50 of 1,056 genes examined became either up- or down-regulated.

Conversely, Fra-1 knockdown altered prominently the morphology, anchorage-independent growth, tumorigenic potential, and Fra-1 effector expression, such as vascular endothelial growth factor D, in HGG cells. For example, cells transfected with antisense fra-1 showed shorter cellular processes than the control cells that did not grow in agar, and their tumorigenic potential was significantly diminished. Thus, Fra-1 may likely play an important role in the maintenance/progression of malignant gliomas and potentially represents a new target for therapeutic interventions.

L12 ANSWER 2 OF 6 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2003:492648 Document No.: PREV200300487100. Epigenetics in high-grade astrocytomas: Opportunities for prevention and detection of brain tumors. **Debinski, Waldemar** [Reprint Author]; Gibo, Denise; Mintz, Akiva. Section of Neurosurgery, Department of Surgery, College of Medicine, Pennsylvania State University, 500 University Drive, H110, Hershey, PA, 17033-0850, USA. wdebinski@psu.edu. Verma, Mukesh [Editor, Reprint Author]; Dunn, Barbara K. [Editor, Reprint Author]; Umar, Asad [Editor, Reprint Author]. (2003) pp. 232-242. Epigenetics in cancer prevention: Early detection and risk assessment. print. Publisher: New York Academy of Sciences, 2 East 63rd Street, New York, NY, 10021, USA. Series: Annals of the New York Academy of Sciences.
Meeting Info.: Workshop on Epigenetics in Cancer Prevention: Early Detection and Risk Assessment. Bethesda, MD, USA. December 03-04, 2001. National Institutes of Health (NIH).
ISSN: 0077-8923 (ISSN print). ISBN: 1-57331-430-7 (cloth). Language: English.

L12 ANSWER 3 OF 6 MEDLINE on STN DUPLICATE 2
2003204925. PubMed ID: 12724228. Epigenetics in high-grade astrocytomas: opportunities for prevention and detection of brain tumors. **Debinski Waldemar**; Gibo Denise; Mintz Akiva. (Department of Neurosurgery, Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033-0850, USA.. wdebinski@psu.edu) . Annals of the New York Academy of Sciences, (2003 Mar) 983 232-42. Ref: 60. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.
AB Human high-grade astrocytomas (HGA) are the most prevalent incurable brain tumors. We found that the vast majority of HGA patients overexpress a restricted receptor for an immune regulatory cytokine, interleukin 13 (IL-13). Interestingly, the HGA-associated restricted receptor protein IL-13Ralpha2 is expressed in the testes, and its gene is localized to chromosome X. These mirror the expression pattern and genomic localization of cancer/testes tumor antigens (CTA). Hypothetical considerations and now experimental evidence are beginning to point towards epigenetics, and DNA methylation alterations in particular, as being responsible for the appearance in cancer of CTA, including IL-13Ralpha2. In line with our interest in the X chromosome and oncogenesis, we have identified a new ubiquitous angiogenic factor in HGA, a vascular endothelial growth factor-D (**VEGF-D**). We have also demonstrated that the activating protein-1 (AP-1) family of transcription factors play a potentially critical role in the progression of gliomas by eliciting uncontrolled upregulation of **VEGF-D** and other compounds essential for cancer cell proliferation, tumorigenesis, and infiltration. The possibility exists that an unopposed constitutive increase in AP-1 activity in HGA is related to epigenetic silencing of the inhibitors of AP-1 activity. These phenomena offer potential targets for exploitation in either prevention or early detection of brain tumors. For example, anticancer vaccines against shared CTA could help in prevention of HGA development. Furthermore, drugs with anti-AP-1 activity could be effective in preventing formation/progression of HGA, or progression from less malignant lower grade gliomas to HGA. Also, circulating antibodies against CTA and factors that are AP-1 regulated may provide a useful tool in early detection of brain tumors or for monitoring their progression following initial treatment.

L12 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
2002:637486 Document No. 137:164115 **VEGF-D** expression in brain cancer in relation to diagnosis and treatment. **Debinski, Waldemar**; Gibo, Denise M. (The Penn State Research Foundation, USA). PCT Int. Appl. WO 2002064097 A2 20020822, 43 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US5044 20020212. PRIORITY: US 2001-PV268089 20010212.

AB **VEGF-D** serves as a target for diagnosing and treating glioblastoma multiforme and related brain cancers. Cancer in a brain tissue sample is detected by analyzing expression of **VEGF-D** in the sample. Brain cancer is treated by modulating **VEGF-D** gene expression in cells of the cancer, and by inhibiting angiogenesis associated with the cancer by interfering with **VEGF-D** binding to a **VEGF-D** receptor.

L12 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
2003:439275 Document No. 139:83053 **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. [Erratum to document cited in CA136:322910]. **Debinski, Waldemar**; Slagle-Webb, Becky; Achen, Marc G.; Stacker, Steven A.; Tulchinsky, Eugene; Gillespie, G. Yancey; Gibo, Denise M. (Division of Neurosurgery/H110, Pennsylvania State University College of Medicine, Hershey, PA, 17033-0850, USA). Molecular Medicine (Baltimore, MD, United States), 7(12), 861 (English) 2001. CODEN: MOMEF3. ISSN: 1076-1551. Publisher: Johns Hopkins University Press.

AB On the cover, "mutliforme" should be "multiforme".

L12 ANSWER 6 OF 6 MEDLINE on STN DUPLICATE 3
2002052394. PubMed ID: 11778649. **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. **Debinski W**; Slagle-Webb B; Achen M G; Stacker S A; Tulchinsky E; Gillespie G Y; Gibo D M. (Division of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psu.edu) . Molecular medicine (Cambridge, Mass.), (2001 Sep) 7 (9) 598-608. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.

AB BACKGROUND: Glioblastoma multiforme (GBM) is a hypervascularized and locally infiltrating brain tumor of astroglial origin with a very poor prognosis. An X-linked c-fos oncogene-inducible mitogenic, morphogenic, and angiogenic factor, endothelial growth factor-D (**VEGF-D**), is the newest mammalian member of VEGF family. We analyzed **VEGF-D** in GBM because of its high angiogenic potential and its linkage to the X chromosome. MATERIALS AND METHODS: Nonmalignant brain and GBM tissue sections as well as GBM cell lines were analyzed by immunofluorescence for the expression of **VEGF-D**, factor VIII (endothelial cell marker), glial-fibrillary acidic protein (GFAP) (astrocytic cell lineage cytoplasmic marker), and several Fos family transcription factors, including c-Fos and Fra-1. The proteins were also detected by Western blots. The differences between genotypes of normal brain and GBM cells were examined by cDNA microarrays. RESULTS AND CONCLUSIONS: GBM expressed ubiquitously **VEGF-D**, which colocalized with GFAP. Contrary to our expectations, low levels of c-Fos were detected in GBM cells. However, we identified another Fos family member, Fra-1, together with its transcriptional activation partner, c-Jun, as being stably up-regulated in GBM cells. Furthermore, we demonstrated that a fra-1 transgene induced **VEGF-D** expression in cultured cells and GBM cell stimulation evoked a sustained increase in both Fra-1 and **VEGF-D** levels. This study

reveals that an up-regulation of AP-1 factors may be a hallmark of GBM. Because **VEGF-D** activates VEGF receptor 2 and 3, receptors important for tumor angiogenesis, it may represent an X-linked/AP-1-regulated onco-angiogen in human GBM. The **VEGF-D** system and AP-1 activity appear to be very attractive targets for new molecular diagnostics and rational molecular anti-cancer therapies.

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L3   ANSWER 1 OF 6  SCISEARCH  COPYRIGHT (c) 2005 The Thomson Corporation  on
     STN                                                    DUPLICATE 1
2005:428915   The Genuine Article (R) Number: 917EQ. Fos-related antigen 1
     modulates malignant features of glioma cells.  Debinski W (Reprint);
     Gibo D M. Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor
     Ctr Excellence, Comprehens Canc Ctr, Med Ctr Blvd, Winston Salem, NC 27157
     USA (Reprint); Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor Ctr
     Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest
     Univ, Sch Med, Dept Radiat Oncol, Brain Tumor Ctr Excellence, Comprehens
     Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest Univ, Sch Med, Dept
     Canc Biol, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem,
     NC 27157 USA. debinski@wfubine.edu. MOLECULAR CANCER RESEARCH (APR 2005)
     Vol. 3, No. 4, pp. 237-249. ISSN: 1541-7786. Publisher: AMER ASSOC CANCER
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RESEARCH, 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA.
Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Malignant gliomas, and high-grade gliomas (HGG) in particular, are non metastasizing but locally infiltrating, hypervascularized brain tumors of poor prognosis. We found previously that a c-fos-inducible vascular endothelial growth factor D is ubiquitously up-regulated in HGG grade IV, glioblastoma multiforme, and that glioblastoma multiforme overexpress Fos-related antigen 1 (Fra-1) rather than the c-Fos. We have thus become interested in the role Fra-1 may play in malignant glioma progression/maintenance, because Fra-1 has the capacity to modulate transcription of a variety of target genes. In this work, we have analyzed the biological effects of ectopic Fra-1 expression or Fra-1 knockdown in malignant glioma cells. Ectopic Fra-1 induced prominent phenotypic changes in all three malignant glioma cell lines examined: H4, U-87 MG, and A-172 MG. These changes were reflected in cells becoming more elongated with larger number of cellular processes. Furthermore, Fra-1 transgene caused H4 cells, which do not form tumor xenografts, to regain tumorigenic capacity. The genotype of these cells changed too, because 50 of 1,056 genes examined became either up- or down-regulated. Conversely, Fra-1 knockdown altered prominently the morphology, anchorage-independent growth, tumorigenic potential, and Fra-1 effector expression, such as vascular endothelial growth factor D, in HGG cells. For example, cells transfected with antisense fra-1 showed shorter cellular processes than the control cells that did not grow in agar, and their tumorigenic potential was significantly diminished. Thus, Fra-1 may likely play an important role in the maintenance/progression of malignant gliomas and potentially represents a new target for therapeutic interventions.

L3 ANSWER 2 OF 6 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2003:492648 Document No.: PREV200300487100. Epigenetics in high-grade astrocytomas: Opportunities for prevention and detection of brain tumors. Debinski, Waldemar [Reprint Author]; **Gibo, Denise**; Mintz, Akiva. Section of Neurosurgery, Department of Surgery, College of Medicine, Pennsylvania State University, 500 University Drive, H110, Hershey, PA, 17033-0850, USA. wdebinski@psu.edu. Verma, Mukesh [Editor, Reprint Author]; Dunn, Barbara K. [Editor, Reprint Author]; Umar, Asad [Editor, Reprint Author]. (2003) pp. 232-242. Epigenetics in cancer prevention: Early detection and risk assessment. print. Publisher: New York Academy of Sciences, 2 East 63rd Street, New York, NY, 10021, USA. Series: Annals of the New York Academy of Sciences.
Meeting Info.: Workshop on Epigenetics in Cancer Prevention: Early Detection and Risk Assessment. Bethesda, MD, USA. December 03-04, 2001. National Institutes of Health (NIH).
ISSN: 0077-8923 (ISSN print). ISBN: 1-57331-430-7 (cloth). Language: English.

L3 ANSWER 3 OF 6 MEDLINE on STN DUPLICATE 2
2003204925. PubMed ID: 12724228. Epigenetics in high-grade astrocytomas: opportunities for prevention and detection of brain tumors. Debinski Waldemar; **Gibo Denise**; Mintz Akiva. (Department of Neurosurgery, Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033-0850, USA.. wdebinski@psu.edu) . Annals of the New York Academy of Sciences, (2003 Mar) 983 232-42. Ref: 60. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB Human high-grade astrocytomas (HGA) are the most prevalent incurable brain tumors. We found that the vast majority of HGA patients overexpress a restricted receptor for an immune regulatory cytokine, interleukin 13 (IL-13). Interestingly, the HGA-associated restricted receptor protein IL-13Ralpha2 is expressed in the testes, and its gene is localized to chromosome X. These mirror the expression pattern and genomic localization of cancer/testes tumor antigens (CTA). Hypothetical considerations and now experimental evidence are beginning to point towards epigenetics, and DNA methylation alterations in particular, as

being responsible for the appearance in cancer of CTA, including IL-13Ralpha2. In line with our interest in the X chromosome and oncogenesis, we have identified a new ubiquitous angiogenic factor in HGA, a vascular endothelial growth factor-D (**VEGF-D**). We have also demonstrated that the activating protein-1 (AP-1) family of transcription factors play a potentially critical role in the progression of gliomas by eliciting uncontrolled upregulation of **VEGF-D** and other compounds essential for cancer cell proliferation, tumorigenesis, and infiltration. The possibility exists that an unopposed constitutive increase in AP-1 activity in HGA is related to epigenetic silencing of the inhibitors of AP-1 activity. These phenomena offer potential targets for exploitation in either prevention or early detection of brain tumors. For example, anticancer vaccines against shared CTA could help in prevention of HGA development. Furthermore, drugs with anti-AP-1 activity could be effective in preventing formation/progression of HGA, or progression from less malignant lower grade gliomas to HGA. Also, circulating antibodies against CTA and factors that are AP-1 regulated may provide a useful tool in early detection of brain tumors or for monitoring their progression following initial treatment.

L3 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
2002:637486 Document No. 137:164115 **VEGF-D** expression in brain cancer in relation to diagnosis and treatment. Debinski, Waldemar; **Gibo, Denise M.** (The Penn State Research Foundation, USA). PCT Int. Appl. WO 2002064097 A2 20020822, 43 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US5044 20020212. PRIORITY: US 2001-PV268089 20010212.

AB **VEGF-D** serves as a target for diagnosing and treating glioblastoma multiforme and related brain cancers. Cancer in a brain tissue sample is detected by analyzing expression of **VEGF-D** in the sample. Brain cancer is treated by modulating **VEGF-D** gene expression in cells of the cancer, and by inhibiting angiogenesis associated with the cancer by interfering with **VEGF-D** binding to a **VEGF-D** receptor.

L3 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
2003:439275 Document No. 139:83053 **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. [Erratum to document cited in CA136:322910]. Debinski, Waldemar; Slagle-Webb, Becky; Achen, Marc G.; Stacker, Steven A.; Tulchinsky, Eugene; Gillespie, G. Yancey; **Gibo, Denise M.** (Division of Neurosurgery/H110, Pennsylvania State University College of Medicine, Hershey, PA, 17033-0850, USA). Molecular Medicine (Baltimore, MD, United States), 7(12), 861 (English) 2001. CODEN: MOMEF3. ISSN: 1076-1551. Publisher: Johns Hopkins University Press.

AB On the cover, "mutliforme" should be "multiforme".

L3 ANSWER 6 OF 6 MEDLINE on STN DUPLICATE 3
2002052394. PubMed ID: 11778649. **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. Debinski W; Slagle-Webb B; Achen M G; Stacker S A; Tulchinsky E; Gillespie G Y; **Gibo D M.** (Division of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psu.edu) . Molecular medicine (Cambridge, Mass.), (2001 Sep) 7 (9) 598-608. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.

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=> s l1 and VEGF
L4          14 L1 AND VEGF

=> s l4 and brain tumor
L5          12 L4 AND BRAIN TUMOR

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PROCESSING COMPLETED FOR L5
L6            4 DUP REMOVE L5 (8 DUPLICATES REMOVED)

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L6   ANSWER 1 OF 4  SCISEARCH  COPYRIGHT (c) 2005 The Thomson Corporation  on
     STN                                                  DUPLICATE 1
2005:428915   The Genuine Article (R) Number: 917EQ. Fos-related antigen 1
     modulates malignant features of glioma cells. Debinski W (Reprint);
     Gibo D M. Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor
     Ctr Excellence, Comprehens Canc Ctr, Med Ctr Blvd, Winston Salem, NC 27157
     USA (Reprint); Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor Ctr
     Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest
     Univ, Sch Med, Dept Radiat Oncol, Brain Tumor Ctr Excellence, Comprehens
     Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest Univ, Sch Med, Dept
     Canc Biol, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem,
     NC 27157 USA. debinski@wfubine.edu. MOLECULAR CANCER RESEARCH (APR 2005)
     Vol. 3, No. 4, pp. 237-249. ISSN: 1541-7786. Publisher: AMER ASSOC CANCER
     RESEARCH, 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA.
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---Logging off of STN---

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